UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	**MDL No. 2875**
THIS DOCUMENT RELATES TO ALL CASES	**HON. ROBERT B. KUGLER** **CIVIL NO. 19-2875 (RBK)(KMW)**

PLAINTIFFS' REPLY IN SUPPORT OF *DAUBERT* MOTION TO EXCLUDE CLASS CERTIFICATION OPINIONS OF ERIC SHEININ, PH.D.

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I. INTRODUCTION

Plaintiffs' opening Motion explained that Dr. Sheinin unabashedly offered the baseless opinions that, despite being contaminated with potent human carcinogens NDMA and NDEA, Mylan's VCDs met their DMF and USP specifications and were therefore the "same" as their Reference Listed Drugs, DIOVAN® and EXFORGE® ("the RLDs"). That is because the DMF and USP specifications are silent on NDMA/NDEA content – as if that means that genotoxic impurities are permitted since not explicitly excluded in the specifications. In fact, for Dr. Sheinin, it would not even change his opinion if a single dose was "guaranteed to kill" the patient; Mylan's VCDs would still be the same as the RLD in his opinion as long as it met the DMF or USP specification. (Pls' Mot., at 11.) This of course makes no sense; our prescription drug regulatory landscape does not have such a loophole that would permit mass poisonings.

The "backdrop" (Mylan Opp'n, at 5) that Dr. Sheinin constructs to reach these illogical conclusions does not fit the facts of this litigation (which Dr. Sheinin did not even bother to learn) and is premised on fundamental regulatory misinterpretations. Specifically, Dr. Sheinin constructs a world where: (1) Drug Master File ("DMF") Specifications are conjured out of thin air without reference to any of the work done as part of the actual DMF which Dr. Sheinin did not review; (2) ICH M7 and its predecessor guidance(s) governing genotoxic impurities *including explicitly NDMA/NDEA* simply do not exist; (3) USP Specifications are static and immutable and do not incorporate prohibitions of unapproved genotoxic impurities, which is contrary to Dr. Sheinin's own work at USP in developing the "flexible monograph"; (4) the FDA had not explicitly told Mylan in its official Warning Letter (again, which Dr. Sheinin did not review) that Mylan's VCDs were "adulterated" because of "significant deviations from [cGMPs]" observed relating to Mylan's manufacture of valsartan API including specifically and primarily Mylan's failure to "anticipate[] the presence of NDMA or NDEA impurities based on [Mylan's] assessment of the API

manufacturing process." (Pls' Mot., Ex. 3.) Dr. Sheinin's constructed world is so contrary to undisputed facts that they lack any reliable foundation, and his opinions cannot be reliably offered; they do not fit the facts of the litigation.

It is no wonder that Dr. Sheinin did not review a single internal Mylan document, a single line of deposition testimony in this case, or any of the pertinent regulatory materials including but not limited to ICH M7 or FDA's Orange Book-provided definition of "therapeutic equivalence." He simply could not have offered his opinions had he done so.

And perhaps most significantly for present purposes, neither Mylan nor Dr. Sheinin explain how Dr. Sheinin's opinions relate in any way to disputed class certification issues. His opinions should be excluded.

II. ARGUMENT

A. Mylan Continues to Fail to Explain How Dr. Sheinin's Report Pertains to Any Disputed Class Certification Issue

Tucked away at the very end of its Opposition, Mylan argues that Dr. Sheinin's Report pertains to class certification because Mylan contends it is a "contested issue" as to whether Mylan's VCDs were adulterated or therapeutically equivalent to the RLDs (which will be hard to imagine given that the FDA officially determined Mylan's VCDs to have been adulterated in Warning Letter(s),[1] resulting from serious cGMP violations, and Mylan itself recalled all its VCDs within expiry).

Moreover, the facts *remain* common to all class members in any event. Mylan does not attempt to explain how these purportedly "contested issues" could apply on anything less than a classwide basis. Nor could it.

[1] FDA letter decisions applying the Federal Food Drug & Cosmetic Act ("FDCA") are entitled to judicial deference. *Mylan Labs., Inc. v. Thompson*, 389 F.3d 1272, 1279 (D.C. Cir. 2004)

At a class trial, Plaintiffs will present evidence that Mylan's most significant deviation from cGMPs relating to its VCDs was its failure to conduct adequate quality assurance and risk assessment that would have predicted the formation of NDEA before any of Mylan's VCDs ever reached consumers. The FDA cited that failure as the primary basis for determining Mylan's VCDs were adulterated in its Warning Letter issued to Mylan. (Pls' Mot., Ex. 3 ("Your firm had not anticipated the presence of NDMA or NDEA impurities based on your assessment of the API manufacturing process.").) Those very cGMP violations also form the basis for Mylan's VCDs not being generic equivalents or therapeutic equivalents to the RLD based on the FDA's clear definition of that term. (Pls' Mot., Ex. 6, at 7.)

B. Dr. Sheinin Cannot Reliably Opine that Mylan's VCDs Met Their DMF Specification

1. Mylan Certified in its DMF [redacted]

As stated in Plaintiffs' Motion, Dr. Sheinin himself agreed at his deposition that the DMF specification is not a standalone document, but rather is developed as a result of the work done by the company in the DMF. (Pls' Mot., at 5.) Mylan complains that reviewing the entire DMF would have consisted of thousands of pages, for what Mylan describes as a "narrow" opinion.[2] However, Plaintiffs do not claim that Dr. Sheinin needed to review the entire DMF; he did however need to review the parts that are germane to this litigation including specifically Mylan's DMF's section on genotoxic impurities.

Had Dr. Sheinin reviewed Mylan's DMF section on genotoxic impurities, he would have understood why Mylan's DMF Specification did not include more sensitive tests that can detect

[2] It is disingenuous for Mylan to describe Dr. Sheinin's opinion as "narrow" in the hopes that the Court will let it slide, so to speak. Mylan's proposed use of Dr. Sheinin's opinion belies such a characterization. Mylan's transparent goal is to put forward an argument that its VCDs are the "same" as the brand RLDs, which is core to Mylan's defense. This is despite Mylan's egregious non-compliance with cGMP that directly resulted in Mylan's failure to prevent or detect the creation of high levels of NDMA and NDEA in its VCDs, which are potent human carcinogens.

trace amounts of NDMA or NDEA (e.g., gas or liquid chromatography including as necessary mass spectrometry), and which Mylan had available to them throughout the relevant time period. Put simply, Mylan falsely assured itself and the FDA (which reviewed Mylan's DMF in approving its ANDA applications) that [redacted] and therefore there was no need for more sensitive testing:

[redacted]

(Pls' Mot., Ex. 9, at 82.)

This certification,[3] of course, was provided without adequate quality assurance and risk assessment efforts, and formed part of Mylan's core cGMP failure as identified by the FDA relating to its VCDs: Mylan's failure to anticipate the creation of NDMA/NDEA based on its manufacturing process. (Pls' Mot., Ex. 3.)

In short, Mylan certified in its DMF that the specification for all genotoxic impurities including specifically NDMA/NDEA [redacted].

[3] Mylan accuses Plaintiffs of misrepresenting the record on whether Mylan certified the absence of NDMA/NDEA in its DMF. (Opp'n, at 11.) The referenced guideline "Mylan Valsartan compli[ed] with" as certified by Mylan specifically and explicitly includes "n-nitroso" compounds within its coverage, and actually describes them as "high potency genotoxic carcinogens[.]" Plaintiffs attach that guideline as **Exhibit 1**, which Mylan corporate witness Wayne Talton affirmed was the document being referenced in the DMF genotoxic impurities certification.

2. Had Dr. Sheinin Reviewed Any Internal Mylan Documents or Testimony, He Would Have Learned that the FDA Rejected His Very Premise When It Was Offered by Mylan Itself

And even more damaging to Dr. Sheinin's theory that NDMA/NDEA would be subject to a 0.1% (or 1000ppm) standard under the catch-all "any other impurity" section of the DMF Specification is how the FDA responded to Mylan's attempt to place a specification limit in the DMF specification for NDMA/NDEA.

Mylan had proposed adding a specific test and acceptance criteria for NDMA/NDEA in its DMF Specification, which the FDA rejected flatly. The FDA stated the following in a DMF deficiency letter:

[redacted]

(Pls' Mot., Ex. 5, at 5 (emphasis added).)

Dr. Sheinin's entire premise is undercut. The absence of a specification for NDMA/NDEA does not mean these potent genotoxic carcinogens are treated like non-genotoxic "any other impurities" subject to 1000ppm limits. As specifically relayed to Mylan, the absence of a specification for NDMA/NDEA is because *there is no acceptable specification*. In other words, exactly as Mylan had put it in the DMF proper[redacted].

C. <u>Mylan Completely Fails to Address Dr. Sheinin's Absolute Disregard of ICH M7</u>

Despite protesting Plaintiffs' still-correct characterization that Dr. Sheinin is effectively pretending NDMA/NDEA are not genotoxic, Mylan does not tackle head on why Dr. Sheinin completely failed to consider ICH M7 and its predecessor guidances. In fact, Mylan mentions ICH M7 a total of zero times in its Opposition. That is because there is no good answer.

ICH M7 is the key regulatory guidance for assessing and controlling genotoxic impurities including *explicitly* NDMA/NDEA. Mylan itself certified compliance with a predecessor version of this guidance in its valsartan DMF, as discussed above.

Dr. Sheinin's entire premise of treating NDMA/NDEA as subject to a 0.1% (1000ppm) "any other impurity" limit completely unravels if one simply thinks what would have happened had Mylan done appropriate quality assurance risk assessment and anticipated the creation of NDMA/NDEA in its valsartan API manufacturing process.

Had Mylan not seriously violated quality assurance cGMPs and identified the risk caused by its valsartan manufacturing process, per ICH M7, it may have been required to initiate with the FDA the exact acceptable intake exercise eventually undertaken that led to the setting of acceptable intakes for NDMA and NDEA. Those numbers were 0.3 ppm and 0.083 ppm, respectively. Those numbers are not part of any DMF specification because – in the FDA's own words to Mylan reproduced above – "NDMA and NDEA[] should be absent from angiotensin receptor blocker drug substances and drug products." (Pls' Mot., Ex. 5, at 5.) There is no default acceptable limit for genotoxic impurities, as for other substances, and this undercuts Dr. Sheinin's entire premise.

To distill it down, the DMF specification is simply not the place to look for NDMA/NDEA limits, and that's what Dr. Sheinin gets terribly wrong. Prior to their discovery, [redacted]; after their discovery, the process of setting acceptable intakes is accomplished through ICH M7 and those limits are not made part of the DMF specification. Dr. Sheinin's assertion that they should be treated as "any other impurity" in the DMF Specification subject to a 0.1%/1000ppm limit is utterly devoid of any support in the factual history of the litigation or the applicable laws and regulations.

D. Mylan Retracts Dr. Sheinin's Critique of Dr. Najafi

Mylan states in its Opposition that "Dr. Sheinin offered no opinions regarding therapeutic equivalence in his report." (Opp'n, at 3.) Mylan insists however that Dr. Sheinin does opine on Mylan's VCDs being "generic equivalents" despite their contamination with high levels of NDEA. That is either a retraction of Dr. Sheinin's entire critique of Dr. Najafi's report, or an example of Mylan playing word games with the Court.

As set forth in Plaintiffs' Motion, Dr. Sheinin agreed that therapeutic equivalence is the regulatory touchstone for what is more colloquially referred to as generic equivalence or sameness between an RLD and a generic drug, resulting in them being "interchangeable" in Dr. Sheinin's own words. (Pls' Mot., at 9-10 (citing Dr. Sheinin's testimony).)

And Dr. Sheinin also agreed that compliance with cGMPs is an FDA requirement for a product to be considered a generic or therapeutic equivalent. (Pls' Mot., at 10 (quoting and citing Dr. Sheinin's testimony).)

Accordingly, Dr. Sheinin undercut his own now-retracted opinion that Mylan's VCDs were generic or therapeutic equivalents to the brand RLD. Mylan's VCDs were indisputably adulterated as manufactured in a facility that was engaging in serious cGMP violations, as determined by the FDA. Per the FDA's own definitions of these terms, which Dr. Sheinin agreed with, Mylan VCDs are not generic or therapeutic equivalents to the brand RLD for that reason alone (not to mention the inherent purity and quality issues associated with being contaminated with potent human carcinogens).

The Court should strike Dr. Sheinin's opinion as retracted, undercut by his own testimony, and without basis.

III. CONCLUSION

For the foregoing reasons, Dr. Sheinin should be excluded from offering his opinions.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on June 16, 2022, a true and correct redacted copy of the foregoing was filed and served via the Court's CM/ECF system, and an undredacted version was served on the court and the Defense Executive Committee via email.

/s/ David J. Stanoch
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